Comments of the American Lung Association and the American Lung Association of California

Comment 1:

The American Lung Association is pleased to have the opportunity to comment on the draft report, "Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant, November 2003." First, we would like to applaud the California Air Resources Board (CARB) and the Office of Environmental Health Hazard Assessment (OEHHA) for their leadership and significant contributions to the scientific evidence regarding the detrimental health effects and harms of environmental tobacco smoke (ETS). This 2003 report builds on the scientific evidence outlined in the 1997 report, by updating the scientific understanding of the exposure and health impacts significantly. As a leading public health organization, the American Lung Association appreciates the volume of data that was collected and synthesized for the draft report.

A Toxic Air Contaminant is defined in Health and Safety Code section 39655 as: "an air pollutant which may cause or contribute to an increase in mortality, in serious illness, or which may pose a present or potential hazard to human health." The American Lung Association believes that based on the fact that there are more than 4000 chemicals in ETS, including 69 that are carcinogenic, the case is clear that ETS should be identified as a toxic air contaminant under California law.

While ETS is clearly linked to number of other health problems, the American Lung Association's comments will be limited to the impacts on respiratory health only. For over twenty years, the evidence has been building on the causal associations between environmental tobacco smoke and lung cancer and other respiratory effects. In 1982, the U.S. Surgeon General first raised concerns that toxins present in tobacco smoke might be causing lung cancer not only in those who smoke, but also in those who involuntarily breathe secondhand smoke. It stated, "although the currently available evidence is not sufficient to conclude that passive smoking causes lung cancer in nonsmokers, the evidence does raise concerns about a possible serious public health problem."

Scientific research into this concern led the U.S. Surgeon General to report compelling evidence in 1986, which was confirmed by research by the National Research Council and U.S. Environmental Protection Agency, concluding that ETS exposure does cause lung cancer and other respiratory outcomes. Much of the research reported in the Draft Report on ETS exposure and lung cancer amplifies and confirms what has been known and accepted for years. We commend the staff on the thorough compilation of new work that continues to strengthen this link.

Response:

Thank you for your comments.

Comment 2:

We would encourage the Science Advisory Panel to examine the methodology behind the attributed lung cancer deaths in your two reports. Currently the CDC and the 1997 Cal EPA report state that 3000 lung cancer deaths are attributed to ETS nationwide, which first appeared in U.S. EPA's 1993 analysis. We understand that this number may be outdated and underestimate the risk, but the attributable incidence and death estimates in the Draft Report are considerably higher. We understand that typographical and calculation errors on ES-11 and 7-76 that address this issue will be revised before the Science Advisory Panel reviews the next draft. More discussion of the methodology to reach both the California and national estimates is needed in the final report to justify this disparity and allow for comment. In order to be consistent, we would suggest using lung cancer deaths versus incidence as the point of comparison in Executive Summary Table ES2.

Response:

Thank you for pointing out these problems of which we were also aware. Errors in the original draft have been corrected. We have recalculated the attributable risk using the same methods that were utilized in the U.S. EPA 1992 estimates. These methods have undergone rigorous review and have been well accepted. The increase in risk noted in our new calculations comes largely from demographic changes during the interim. These calculations are spelled out in detail in the revised draft document.

Comment 3:

Another important topic reviewed in the Cal EPA report was the association of ETS with asthma exacerbations and induction. The American Lung Association is very interested in the scientific evidence that demonstrates linkages to asthma exacerbation, increases in asthma symptoms and induction of asthma from exposure to environmental tobacco smoke. We believe that the science is conclusive that ETS is a risk factor in the exacerbation of asthma in both children and adults. However, our review of the data in the Draft Report lead us to believe that the link to asthma induction in adults requires further scientific study to merit conclusive findings at this time. We encourage the Scientific Advisory Panel's investigation and comments on the staff report's recommendation to move from suggestive in the 1997 report to conclusive in this draft report regarding asthma induction in adults.

Response:

While we understand that good scientists and epidemiologists are appropriately reluctant to assign the term causative to an exposure without substantial and convincing evidence, we believe that indeed this hurdle has been cleared in the case of ETS and adult onset asthma. Some of the

key factors are outlined below and our discussion has been expanded similarly in the revised document.

Examination of the Hill criteria supports a causal association between ETS exposure and adult asthma onset. Several studies demonstrated an exposure-response relationship between ETS exposure and the risk of developing new-onset adult asthma or wheezing, which supports the case for a causal relationship. Exposure-response relationships were observed for total daily duration of ETS exposure (Leuenberger et al. 1994), number of smokers in the environment (Leuenberger et al. 1994; Hu et al. 1997), duration of exposure to smoker (Leuenberger et al. 1994; Kunzli et al. 2000; Iribarren et al. 2001; Janson et al. 2001), duration of working with a smoker (Greer et al. 1993; McDonnell et al. 1999), measured nicotine levels (Eisner et al. 2001), and an ETS exposure index that incorporates both intensity and duration of exposure(Jaakkola et al. 1996). Taken together, these studies demonstrate exposure-response relationships that are consistent with a causal relationship between ETS exposure and adult asthma onset.

The temporal relationship between ETS exposure and the development of asthma or asthma-like symptoms was clearly delineated in most studies. In particular, studies have defined ETS exposure in childhood (Larson 2001), a defined period prior to the diagnosis of asthma (Flodin 1995, Thorn 2001, Hu 1997, Greer 1993, McDonnell 1999), or a defined period prior the development of asthma-like symptoms (Withers 1998, Strachan 1996). In these studies, exposure to ETS clearly predated the development of asthma.

The consistency of study findings also supports a causal relationship between ETS exposure and asthma morbidity. In samples drawn from different populations, ranging from clinical to population-based samples, and different countries around the world, investigators have observed the association between ETS exposure and new-onset asthma. The relationship between ETS exposure and asthma has been observed in a variety of study designs, including cross-sectional, case-control, and cohort studies. Exposure in different environments, such as home and work, has also been linked with asthma. The consistency of findings linking ETS exposure with different related respiratory health outcomes, including new-onset asthma and wheezing, supports a causal association between ETS exposure and adult onset asthma.

Because ETS contains potent respiratory irritants, exposure may adversely affect bronchial smooth muscle tone and airway inflammation (California Environmental Protection Agency 1997). Studies linking ETS exposure with a decrement in pulmonary function support the biologic plausibility of ETS-related asthma onset. Taken together, studies of adults support a small but significant deleterious effect of ETS on pulmonary function (Hole et al. 1989),(Comstock et al. 1981),(Ng et al. 1993),(Masi et al. 1988),(O'Connor et al. 1987)-(Xu and Li 1995) (Schilling et al. 1977; Kauffmann et al. 1989) (Brunekreef et al. 1985)-(Abbey et al. 1998; Carey et al. 1999) (Jaakkola et al. 1995) (Dimich-Ward et al. 1998) (Eisner et al. 1998; Eisner 2002).

The studies reviewed also demonstrate coherence in the association between ETS exposure and asthma morbidity. ETS exposure has been associated with new-onset asthma, whether defined as self-reported physician diagnosed asthma or a clinical asthma diagnosis. Furthermore, ETS exposure is associated with related health outcomes, including chronic respiratory disease and respiratory symptoms such as wheezing, cough, and dyspnea. The coherence of these findings among diverse respiratory outcomes supports a causal association.

A key issue is distinguishing the development of incident adult-onset asthma, as opposed to exacerbation of previously established disease. Several studies directly support the impact of ETS exposure and incident adult asthma (Thorn 2001, Hu 1997, Greer 1993, McDonnell 1999, and Jaakkola 2003). Other studies have prospectively examined the relation between ETS exposure and incident wheezing (Withers 1998, Strachan1996). Fortunately, since the writing of the original draft of our document, a very useful paper has been published that provides the kind of evidence that has been difficult to obtain. This is a study in Finland by M. Jaakkola, et al (AJPH, 2003;93:2055-2060), which was a large population based incident case-control design in a system that had the advantage of being able to define all incident cases of new onset asthma diagnosis. Diagnosis was based on clinical examination and included lung function measurement. Recruitment was aided by being able to identify via National Social Insurance records all patients who had received reimbursement for asthma medications and included 521 newly diagnosed case patients out of a population of over 440,000. The risk of new onset asthma in adults age 21-63 was doubled in those exposed to workplace ETS (OR 2.16, CI 1.26, 3.72) and

nearly five fold in those with home exposure (OR 4.77, CI 1.29-17.7). Cumulative exposure over a lifetime at work and at home increased risk. This study indicates that cumulative lifetime exposure to ETS increases the risk of adult-onset asthma. A summary of this paper is included in the revised document.

The population-based study by Jaakkola and colleagues provides the strongest evidence to date that links ETS exposure to incident adult asthma. The investigators used a systematic surveillance system to identify newly diagnosed adult asthma cases in a region of Finland and to exclude pre-existing asthma cases. ETS exposure assessment ascertained exposure history during the past 12 months and the entire lifetime. Taken together, these studies indicate that ETS exposure is associated with the subsequent development of incident adult asthma.

In sum, studies of ETS and adult-onset asthma have controlled for bias and confounding. They have demonstrated temporality, exposure-response relationship, consistency, coherence, and biologic plausibility, supporting a causal relationship.

Comment 4:

The issue of asthma induction in children is more complex. There is no doubt that higher rates of asthma exist in children of smoking parents. Prenatal exposure from a smoking mother does appear to alter lung growth and development *in utero* as the inhaled tobacco crosses the placenta. This would suggest a causal relationship between prenatal maternal smoking and asthma induction in children. Many of the studies in the Draft Report do not seem to distinguish between pre- and postnatal exposure. While the Lung Association supports the conclusive link of asthma induction in children, we would welcome a more robust examination of data that differentiates between pre- and postnatal exposure. It is very difficult to prove causal damage and the research is not as clear as to whether postnatal ETS exposure triggers an attack in a child who is predisposed to asthma or induces the first asthma attack of an existing condition. (Given the suggestive link between paternal smoking preconception and childhood cancers, this might also be another area of research to pursue in relation to childhood asthma induction in non-smoking mothers as well.)

Response:

The current document "Health Effects of Environmental Tobacco Smoke" is not intended as a stand-alone volume but rather as additional information to update the 1997 document (see Section 1.0, chapter1, part B). The issue of induction of childhood asthma was dealt with in the 1997 volume and the conclusion that ETS exposure causes induction of childhood asthma was

supported by the review by the Scientific Review Panel. The additional evidence presented in this update is supportive of the previous findings. The paragraph below summarizes the previous conclusion, which in part was based upon a meta-analysis performed by OEHHA and included in the 1997 document:

> "There appears to be a simple biological gradient of effect (or dose-response) in studies that collected data on levels of smoking, where effects were detectable only when the mother smoked 10 or more cigarettes per day (*e.g.*, Martinez *et al.* 1992). This finding suggests that a threshold of ETS exposure intensity is required in order to evoke this response. The temporal relation between childhood asthma and parental smoking is not at issue here, since asthma in children is unlikely to precede active smoking by their parents. However, it might be argued that, since the association seems to be strongest between maternal smoking and asthma prevalence in pre-school children, the key exposures may have taken place *in utero*. Several recent studies suggest that pre-natal exposures may cause persistent decrements in lung growth and development (Cunningham *et al.* 1994, 1995, Hanrahan *et al.* 1992). It is possible that pre-natal effects may play a role as well in the etiology of childhood asthma. However, the studies by Chen (1986, 1988, 1989), showing effects of paternal smoking alone, as well as studies of ETS exposure linked to increased risks of asthma in nonsmoking adults (Leuenberger *et al.*, 1994), indicate that post-natal exposures can be sufficient to elicit this outcome. Development of asthma as a result of ETS exposure is "coherent" with other investigations demonstrating that both active and passive exposure to cigarette smoke are associated with increases in airway responsiveness, which (as noted above) is a characteristic feature of asthma. The biological plausibility of this relationship is strong: (1) ETS exposure predisposes young children to an increased risk of repeated respiratory infection, a recognized risk factor for the development of asthma; (2) ETS causes airway hyperresponsiveness; (3) ETS may increase the risk of childhood atopy and of increased circulating allergy-related antibodies (IgE), enhancing the probability of allergic asthma; (4) cigarette smoke causes airway inflammation in active smokers (Niewohner, 1974) and may have similar (but lower-level) effects in people exposed to sidestream smoke. Taken as a whole, the epidemiologic evidence of causation is compelling."

There appears in the literature both evidence of an increase in incidence of asthma in children whose mothers smoked during pregnancy and then had additional exposure postnatally (over those not postnatally exposed) and in children who were not exposed to maternal smoking in utero but were exposed only postnatally. To address the request for further evaluation of this data we are including a meta-analysis conducted by OEHHA (updated from the 35 studies reviewed in the 1997 document to include 85 studies) of the literature in the final draft. The table below from this new analysis summarizes the four studies in which a statistically significant

increase in asthma was found in children who had only postnatal exposure and for whom the studies controlled for child's allergies or a family history of allergy and child's own smoking.

Table 1: Studies that examined postnatal ETS exposure and found a statistically significant relationship between postnatal exposures to ETS only and the development of asthma in children

Study	Design	post natal only	lcl	ucl	both	lcl	ucl	ages	Exposure measure	issue
Agabiti Current asthma	Nested case control	1.25	1.03	1.52	1.83	1.19	2.80	6-7	Mother was ex smoker	Ex smoker
Azizi 1995 current asthma	Case control	1.91	1.13	3.21	----	----	----	1m - 5	No mothers smoked, others smoked in the same bedroom as child	Others smoked in same bedroom
Neuspiel wheezy bronch.	Prospective cohort	2.16	1.19	3.93	1.52	1.27	1.82	0-10	Lifetime exposure	Lifetime exposure
Mannino Current asthma	Cross sectional	4.4	1.40	13.5	7.3	2.5	21.2	4-6	highest tertile of cotinine	Younger child high exposure

Other metrics within some of these studies as well as other studies that also controlled for these important factors do not show a statistically significant association and are summarized in the table 2 below.

We feel that the discrepancies between the findings in these two tables are understandable and that several factors have been identified by the authors of the cited studies themselves that explain why some observe effects and others do not. In general, those studies that were able to identify higher (Mannino, Azizi) and longer exposures (Mannino, Neuspiel) identified significant associations. High exposure categories (by history or cotinine) and lifetime exposure are less prone to misclassification. Also, significant findings may be more difficult to identify in older children when their exposure is defined as "current ETS exposure" as it is in many studies. Current smoking habits are much more likely to reflect the smoking habits of mothers in early childhood but may misclassify the early childhood exposures to ETS in older children (i.e.

mothers that quit during pregnancy may have started smoking again later in their child's life) (Mannino, Agabitti).

Table 2: Studies that examined postnatal ETS exposure but did not find a statistically significant relationship between postnatal exposures to ETS only and the development of asthma in children.

Study	Design	post natal only	lcl	ucl	both	lcl	ucl	ages	Exposure measure	issue
Mannino Ever asthma	Cross sectional	0.8	0.30	2.1	0.7	0.3	1.7	7-11	highest tertile of cotinine	Ever asthma, older child
Mannino Current asthma	Cross sectional	0.9	0.40	2.5	0.6	0.2	1.7	7-11	highest tertile of cotinine	Older child
Ehrlich 1996 Current asthma/wheeze	Nested case control	0.8	0.45	1.44				7-9	Mother current smoker, cotinine levels in child more closely associated with # of HH smokers	Few mothers smoked more than 10 cigs/d Older child
Agabiti Current asthma	Nested case control	1.02	0.85	1.21	0.69	0.45	1.06	13-14	Mother was ex smoker	Older child
Mannino Ever asthma	Cross sectional	2.2	0.90	5.0	4.4	1.4	13.5	4-6	highest tertile of cotinine	Ever asthma
Agabiti Current asthma	Nested case control	1.12	0.93	1.35	1.62	1.34	1.96	6-7	Mother was current smoker	Older child
Agabiti Current asthma	Nested case control	1.15	0.99	1.34	1.22	1.02	1.47	13-14	Mother was current smoker	Older child

We feel that it is a semantic issue as to whether a child who has been exposed in utero and then develops asthma after postnatal ETS exposure can be said to have ETS induced asthma or an uncovering of a pre-existing tendency. Even though postnatal exposure leads to an increased risk among those already primed by prenatal exposure, we would still consider the onset of asthma as induction by ETS.

Below are data from Dr. Mannino's paper (Arch Pediatr Adolesc Med, 2001) that are displayed as his figure 1 in that publication. In this he has clearly separated out children with high continine who were and were not exposed to maternal prenatal smoking (PNS). In the younger age grouping of 4-6 years there is a clear and significant increase in risk of current asthma comparing the highest cotinine tertile with lowest without exposure to PNS. This is exacerbated in those with PNS. For ever asthma, there is an elevated but not statistically significant risk noted. These were not seen in the older ages but as noted above this may be a reflection of current cotinine levels being more reflective of lifetime exposure in early childhood than in later years.

Children 4-6	**N**	**Ever Asthma**	**Current Asthma**
Hi Cot + PNS	248	3.1 (1.1 - 8.8)	7.3 (2.5, 21.2)
Hi Cot - PNS	375	2.2 (0.9, 5.0)	4.4 (1.4, 13.5)
Mod Cot + PNS	51	1.7 (0.2, 17.6)	5.2 (0.6, 47.6)
Mod Cot - PNS	539	0.6 (0.3, 1.3)	0.9 (0.3, 2.4)
Low Cot + PNS	19	2.6 (0.3, 24.0)	1.7 (0.3, 11.1)
Low Cot - PNS	388	1	1

A more complete discussion of the above analysis will be included in our final draft under "child/asthma induction meta-analysis".

Comment 5:

It is becoming increasingly clear that environmental tobacco smoke is a serious toxic air contaminant, affecting the health of millions of Americans. We must continue to respond to the science with aggressive policy and legislation in order to lessen the impact of this deadly substance. We thank the State of California for expending the resources to update the scientific research associated with Environmental Tobacco Smoke and move that it finalize the report as a first step in strengthening protections from ETS.

Response:

Thank you for your review and comments.